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Height in Relation to Dementia Death: Individual-participant Meta-analysis of Eighteen UK Prospective Cohort Studies

RUNNING HEAD: Height in relation to dementia death

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ABSTRACT WORD COUNT: 161

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ABSTRACT

Background: That risk factors measured in middle-age may not fully explain future dementia risk implicates exposures acting earlier in life.

Aims: Height may capture early life illness, adversity, nutrition, and psychosocial stress. We investigated the little-explored association between height and dementia death.

Method: Individual-participant meta-analysis using eighteen prospective general population cohort studies with identical methodologies (baseline 1994-2008; N=181,800).

Results: Mean follow-up of 9.8 years gave rise to 426 and 667 dementia deaths in men and women, respectively. Mean(SD) height for men was 174(7.3)cm, and 161.0(6.8)cm for women.

In analyses taking into account multiple covariates, increasing height was related to lower rates of death from dementia in a dose-response pattern ($p_{\text{trend}} \leq 0.01$). There was evidence of a differential effect by gender ($p_{\text{interaction}} = 0.016$). Thus, the association observed in men (hazard ratio per SD decrease in height; 95%CI: 1.24;1.11-1.39) was markedly stronger than that apparent in women (1.13;1.03-1.24).

Conclusions: Early life circumstances, indexed by adult height, may influence later dementia risk.

Declaration of Interest: none

KEY WORDS: Body height, epidemiology, dementia, meta-analysis, socioeconomic factors

INTRODUCTION

With no current disease-modifying treatments for dementia, there is a pressing need to understand the aetiology of this condition with a view to delaying or preventing its onset. It is evident that known risk factors for dementia measured in middle-age – hypertension, smoking, obesity, and dyslipidaemia – do not seem to fully explain the occurrence of the disease.¹⁻³ This has prompted some recent interest in the pre-adult origins of dementia.⁴

In the absence of cohort studies beginning in childhood with a sufficiently long period of follow up to allow enough individuals to develop dementia in later life, investigators have relied on the distant recall of early life risk factors, such as early parental death and childhood socioeconomic adversity.⁵⁻⁷ This raises concern regarding reporting bias.⁸ Height may be more useful in this context. It is regarded as a marker of early life illness, adversity, nutrition and psychosocial stress,⁹ environmental characteristics that influence brain development which may then impact upon dementia risk.¹⁰ Importantly, while there may be some loss of height in late life, it remains relatively stable from early to late adulthood and may therefore be a reliable marker of early life exposures.

Findings from a small series of cohort studies indicate that lower physical stature is associated with elevated rates of dementia¹¹ and this effect may be different in men and women.¹² However, in general, studies have been underpowered. The fact that the few extant studies are small in scale hampers a detailed examination of the height-dementia association in detail, for example, in exploring threshold effects and planned sub-group analyses of the height-dementia relationship, including by gender.

Accordingly, in this study, we add to the limited evidence base by presenting an individual participant meta-analysis of eighteen large, prospective, general population-based, cohort studies.

Individual participant meta-analysis has several advantages relative to the more commonly used literature-based approach, including: the inclusion of unpublished data so minimising publication bias; a more precise estimate of associations between risk marker and disease than in lesser-powered single studies; reliable information on the ‘shape’ of the association; and a consistent approach to statistical control for plausible covariates. To the best of our knowledge, this is the largest study to date to examine the association between height and dementia and the first individual participant meta-analysis on the topic.

METHODS

Study samples

Participants were taken from the Health Survey for England¹³ (1994-2008) and the Scottish Health Survey¹⁴ (1995, 1998, and 2003), both representative, general population-based health examination studies sampling individuals living in households in the UK. From 1994-2008, eighteen independent, cross-sectional studies with almost identical methodologies were conducted either on an annual (HSE) or occasional (SHS) basis. The majority of study members (88.3%) consented to mortality surveillance by linkage to the UK National Health Service death register. The near identical nature of these surveys, allied with this recent retrospective and prospective linkage of study members to mortality records, makes possible a unique individual participant meta-analysis. Study participants gave full informed consent and ethical approval for data collection was granted by the London Research Ethics Council or the Local Research Ethics Councils.

Participants were visited by a trained interviewer, who measured height and weight, and subsequently by a nurse, who collected biomedical data. The interviewer measured height once with shoes removed (to the nearest millimetre) with the informant stretching to their maximum height. The head was positioned in the Frankfort plane and a portable stadiometer with a sliding

plate, a base plate and three connecting rods marked with a metric measuring scale was used.

Weight was measured using electronic digital scales and, with height, allowed computation of body mass index using the usual formula ($\text{weight}[\text{kg}]/(\text{height}[\text{m}])^2$).

Information on occupational social class was collected during the interview and coded according to the Registrar General classification (professional, intermediate, skilled non-manual, skilled manual, part-skilled, and unskilled), a standard approach in the UK.¹⁵ Age upon leaving full-time education was recorded as <15, 15, 16, 17, 18, >18 years, 'never went to school', and 'still in full-time education'. Ethnic group was based on self-report. Smoking status was classified as never a regular smoker, ex-smoker, and smoker with daily consumption recorded. During the interview, participants were asked whether or not they suffer from a long-standing illness. At the nurse visit, systolic blood pressure was measured with the mean of the second and third readings used in the present analyses. Blood was drawn to measure serum cholesterol.

Ascertainment of Dementia

Causes of death (up to ten) recorded on certificates were coded using the International Classification of Diseases, Ninth (ICD-9) and Tenth (ICD-10) revisions. Any mention of dementia death was identified using codes 290.0 to 290.4, 294.9, 331.0 to 331.2, and 331.9 for ICD-9 and F00, F01, F03, F09, G30 and G31 for ICD-10. In preliminary analyses we examined the impact of using broad (any mention of dementia) and narrow definitions of dementia (where dementia was the underlying cause of death). Since results were essentially the same but the broader definition resulted in greater power (Supplementary Table 1) we used any mention of dementia in all survival analyses.

Dose-response meta-analysis

After ascertaining that the proportional hazards assumption had not been violated we used Cox proportional hazards models¹⁶ to compute study-specific hazard ratios with accompanying 95% confidence intervals for the association between height and dementia death. We report hazard ratios for height quartiles with the tallest group as the referent. With preliminary analyses revealing that the height-dementia association was linear, we also report hazard ratios per one standard deviation (SD) reduction in height (one SD = 6.8cm in women; 7.3cm in men).

Heterogeneity in the effect estimates between studies was examined using the I^2 statistic, which indicates the proportion of the total variation in the estimates that is due to between-studies variation. Preliminary analyses revealed that the I^2 statistic ranged between 0 and 58% so we pooled the study-specific effect estimates and their standard errors in random effects meta-analyses, an approach we have taken in previous analyses.^{15, 17, 18} Calendar time (months) from survey date was the underlying time scale; for participants who did not die from dementia, data were censored at the end of March 2011.

Data for men and women were analysed separately. Models were initially adjusted for age and then additionally for a series of covariates: occupational social class, educational attainment, ethnic group, body mass index, smoking status, and self-reported longstanding illness. We also controlled for birth year to allow for secular increases in height.¹⁹ Data for blood pressure and serum cholesterol were not collected in every survey (see Supplementary Table 2) and were additionally missing for some participants during the survey years when data collection took place; these data therefore only feature in subgroup analyses. We compared the effects of controlling for different confounding and mediating variables on the magnitude of the association by examining the change in hazard ratio rather than a change in significance level.²⁰

Individuals with data missing for one or more variable and those with no missing data were compared using Student's t-test for continuous variables and χ^2 tests for categorical variables. All analyses were conducted using R version 3.0.2. The reporting of our analyses conforms to the STROBE statement.²¹

RESULTS

Figure 1 shows the derivation of the analytical sample. Excluding 1840 individuals missing consent data and 1365 missing survival time reduced the sample size from 222,829 to 219,624. With other exclusions (survey participants who declined mortality follow up or whose height was not measured), the final analytic sample was 181,800 (55% female; mean[SD] age at baseline 45.0[18.0]; among those who died mean[SD] age at death 55.8[17.5]). Further details of the individual cohort studies and individuals who did and did not consent to mortality follow up are provided in Supplementary Tables 2 and 3 respectively.

Baseline characteristics of the sample by height quartile are shown in Table 1. Increasing height was generally associated with a more favourable risk factor profile in both sexes: taller study members were younger, from higher socioeconomic backgrounds, more likely to be white British, had slightly lower body mass index, a lower prevalence of longstanding illness, and lower levels of blood pressure and serum cholesterol. Taller men were also less likely to smoke but the reverse was true of women.

Of the 17,553 deaths recorded during a mean(SD) follow up of 9.8(4.4) years, 1093 were dementia-related. Figure 2 shows the age-adjusted hazard ratios for the association between one SD decrease in height and dementia death in men and women for each cohort study. Overall, there was a 26% increased risk of dementia death per SD decrease in height in men (HR 1.26;

95%CI 1.14-1.40; $P_{\text{trend}} < 0.001$) and 10% increased risk of dementia death in women (1.10; 1.01-1.19; $P_{\text{trend}} = 0.031$).

Table 2 shows the association between height quartile and dementia death after adjustment for covariables. In age-adjusted analyses, there was a dose-response association in both men and women such that lower physical stature was associated with raised dementia mortality rates. There was also some evidence of weaker associations in women than men: a formal test for effect modification was statistically significant at conventional levels (Multivariable adjusted model: $P_{\text{interaction}} = 0.016$). Adjusting for measures of socioeconomic status had a modest attenuating effect on this association.

Sensitivity and sub-group analyses

We conducted a series of sensitivity and sub-group analyses to test the robustness of our results. Data were missing for one or more variable in 34,833 individuals (18.0%). Individuals with complete data for all variables are compared to those with any missing data in Supplementary Table 4. While there were some differences in study characteristics, when we computed age-adjusted hazard ratios using a non-missing sample, it replicated the main findings. Additionally, dropping deaths occurring in the first five years of follow-up to explore reverse causality did not alter our conclusions (Table 2).

DISCUSSION

The main findings of this study are a dose-response association between shorter height and risk of subsequent dementia death. There was some suggestion that this relationship was stronger in men. It was robust to adjustment for a series of covariates including socioeconomic status and extant illness. That we were also able to demonstrate known associations between shorter stature and an increased risk of cardiovascular disease^{22, 23} (age- and sex-adjusted HR per SD decrease in

height 1.11; 95%CI 1.07-1.16) but a decreased risk of cancer²⁴ (0.94; 0.89-0.98) in this meta-analysis gives us confidence in the more novel height-dementia association.

Mechanisms of effect

The fact that the observed association between height and dementia was apparently robust to the adjustment of a series of covariables leads to speculation regarding the mechanisms which might generate this relationship. Clearly height in itself is not a risk factor for dementia; rather, the exposures it captures may be key. In addition to genetic factors, a recent review of epidemiological studies highlighted various socio-environmental determinants of adult height, including early life socioeconomic circumstances, childhood nutrition, chronic psychosocial stress, and chronic illness.¹⁹ Insulin growth factor IGF-1 has been linked to cerebral amyloid²⁵ and, similarly, growth hormone levels, which are correlated with height and also linked to hippocampal function and cognition. Thus, IGF-1 might play a role in the association between height and dementia death.⁴ Furthermore, important exposures may also act *in utero*, but research linking birth characteristics to dementia is sparse.

There is also the possibility that height might be a measure of cognitive and functional reserve²⁶ and a positive association has been demonstrated between height and intelligence,²⁷ which is also related to dementia risk, particularly vascular dementia.^{10,28} A further possibility is a common genotype determining height and dementia risk.

Average height in populations has generally increased in a secular fashion over the last hundred years, with a particularly marked increase in the first quarter of the twentieth century (see Figure 3). The fact that there has been a general improvement of early life circumstances over this same period further supports the hypothesis that height captures something of early life experience

relevant to later dementia risk, particularly in the light of recent studies suggesting that the prevalence²⁹ of dementia might have decreased in recent years.

Given the large sample size of the present study the smaller effect identified in women is unlikely to be explained by statistical instability. One possibility is that physical stature in women is less sensitive to living conditions. That diminishing secular increases in female height have been observed in recent years provides some support for this.¹⁹

Comparison with other literature

The published literature on the association between stature and dementia risk is detailed in Table 3. The present study is the first examining the association between stature and dementia mortality. However, for comparison, research reporting on the association with clinical dementia will be discussed here. In a Medicare study of the association between knee height and arm span and dementia in four areas of the USA, 480 participants developed dementia over a mean 5.4 year follow up.¹² Both measures of shorter stature were associated with a higher risk of dementia in women, but only arm span was associated with dementia risk in men. A study in Israel, only including men, demonstrated an odds ratio of dementia (309 cases) comparing the tallest and shortest height quartiles of 0.51 (0.35-0.74) after adjusting for age, socioeconomic status, and region of birth.¹¹ A study of Japanese Americans in Washington, USA, as part of the Ni-Hon-Sea Project – mainly focusing on head circumference – similarly commented that individuals developing dementia (59 incident cases) were shorter than those who did not go on to develop the condition. However this was not examined in detail.³⁰

Cross-sectional studies also add to the evidence for a link between height and dementia. A study of an older Korean population (N = 746, 110 dementia cases) found an association between shorter leg length and demispan and dementia after adjusting for age and education.³¹ When examining men and women separately their results were only statistically significant in women

but since only 41% of the sample were men, this might be a result of reduced power. Another Korean study (N=235; 46 dementia cases) found an association between decreased height and increased dementia risk (age- and sex-adjusted HR per cm decrease; 95%CI: 1.09; 1.05-1.14) which was attenuated with further adjustment for education, smoking, alcohol, pulse pressure, hypertension, and type 2 diabetes mellitus (1.03; 0.97-1.11).²⁶ The HARMONY study of Swedish Twins conducted a case-control analysis of 310 people with dementia and 3063 controls.³² They found that being more than one standard deviation below the sex-specific mean in height was associated with an odds ratio of dementia of 1.57 (95%CI 1.11-2.22). A case-control study from the USA found a lower risk of Alzheimer's disease in women, adjusted for age and education, but not men.³³ However when they stratified by APOE ε4 status they only found this association in women without that allele (OR 0.88, 95%CI 0.80-0.97). A further Korean study found an association, only in women, between leg length and Alzheimer's disease, after adjustment for age, rural residence in childhood and education.³⁴

There is growing evidence – from studies of variable quality and statistical power – that shorter body stature, measured in a variety of ways, is associated with an increased risk of cognitive decline and dementia in men and women. A number of studies have reported a dose-response association^{11, 12, 33, 35} but the majority have treated height as a continuous measure without demonstrating a linear relationship.^{26, 30, 31, 34, 36, 37} In the present study we were able to demonstrate a statistically significant, dose-response association between decreasing height and dementia death.

One prospective study¹² and two cross-sectional studies^{31, 34} showed a stronger association between height and dementia in women than in men. In the present study we found the converse. It is possible that this disagreement relates to power or to the different outcomes: the studies referred to above used a clinical diagnosis of dementia as their outcome, as opposed to

dementia-related death used in the current study. Details of dementia incidence were not available for our included cohort studies. We are not aware of any studies directly comparing risk factors for dementia incidence and dementia-related mortality.

Limitations

Our large sample was representative of the general population in the UK and was well-characterised in terms of baseline characteristics. This provided sufficient power to allow gender-specific analyses and allowed us to explore the role of a series of explanatory factors. Crucially, this study is well characterised for socioeconomic status (educational attainment and occupational social class) which is a key confounding variable given its association with dementia and height.

This notwithstanding, the data also have their limitations. The number of dementia-related deaths in this study is likely to have been affected by the unavoidable problems of under-diagnosis of dementia in the community,³⁸ under-recording of dementia on death certificates, and diagnoses being inaccurately coded. Non-recording of dementia on death certificates has been highlighted as an important issue but this seems to be improving. A recent study identified that 71.5% of a clinic sample diagnosed with probable Alzheimer disease had dementia correctly recorded on their death certificate.³⁹ There was no association in that sample between correct dementia certification and area deprivation or premorbid IQ estimated by the National Adult Reading Test (unpublished results available on request), suggesting that individuals reported as having dementia on their death certificate are representative of the population of people with diagnosed dementia in the community, at least in terms of intelligence and level of deprivation.

Future research directions

Ideally, a long-term longitudinal study with adult height and relevant covariates measured in early life could be analysed over decades of follow up to investigate this association in more detail, including information on parental height in order to take genetic determinants of height into account. In the absence of such a study, a more detailed investigation of just what it is that height is capturing that is associated with later dementia risk to allow more accurate forecasts of dementia incidence to be calculated.

Conclusion

We have demonstrated a dose-response association between height and later dementia death which was robust to adjustment for a series of covariates. We hypothesise that the mechanism driving this association may be early life circumstances and thus add to the growing evidence for the role of pre-adult factors in later dementia risk. Furthermore, public health policies should continue on a broad front, including pre-school education, breakfast clubs, improved parenting schemes, and vaccination programmes.

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FIGURE 1. Flow chart of participants from initial pooled sample through to analytic sample showing subsequent mortality: individual participant meta-analysis of eighteen cohort studies from the Health Survey for England and the Scottish Health Survey (N = 181,800)

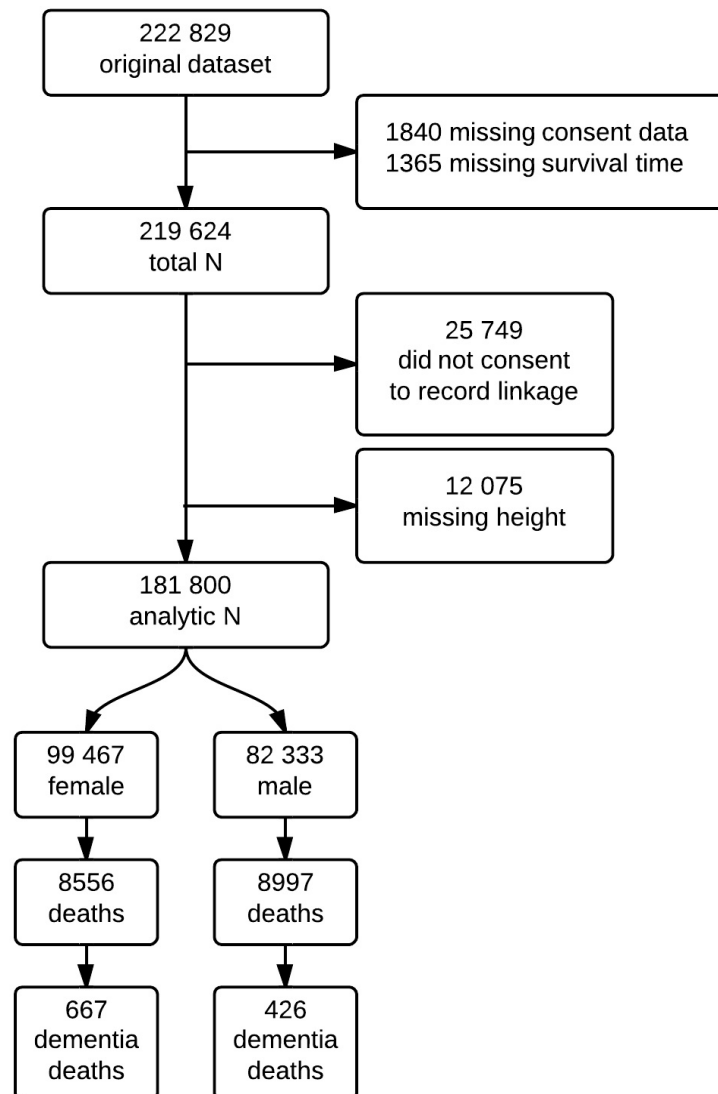


FIGURE 2. Number of participants, total mortality and deaths from dementia by year. Also shown are age- and sex-adjusted hazard ratios with 95% confidence intervals of dementia death per standard deviation lower height by survey year for men (top) and women (bottom): individual participant meta-analysis of eighteen cohort studies from the Health Survey for England and the Scottish Health Survey (N = 181,800)

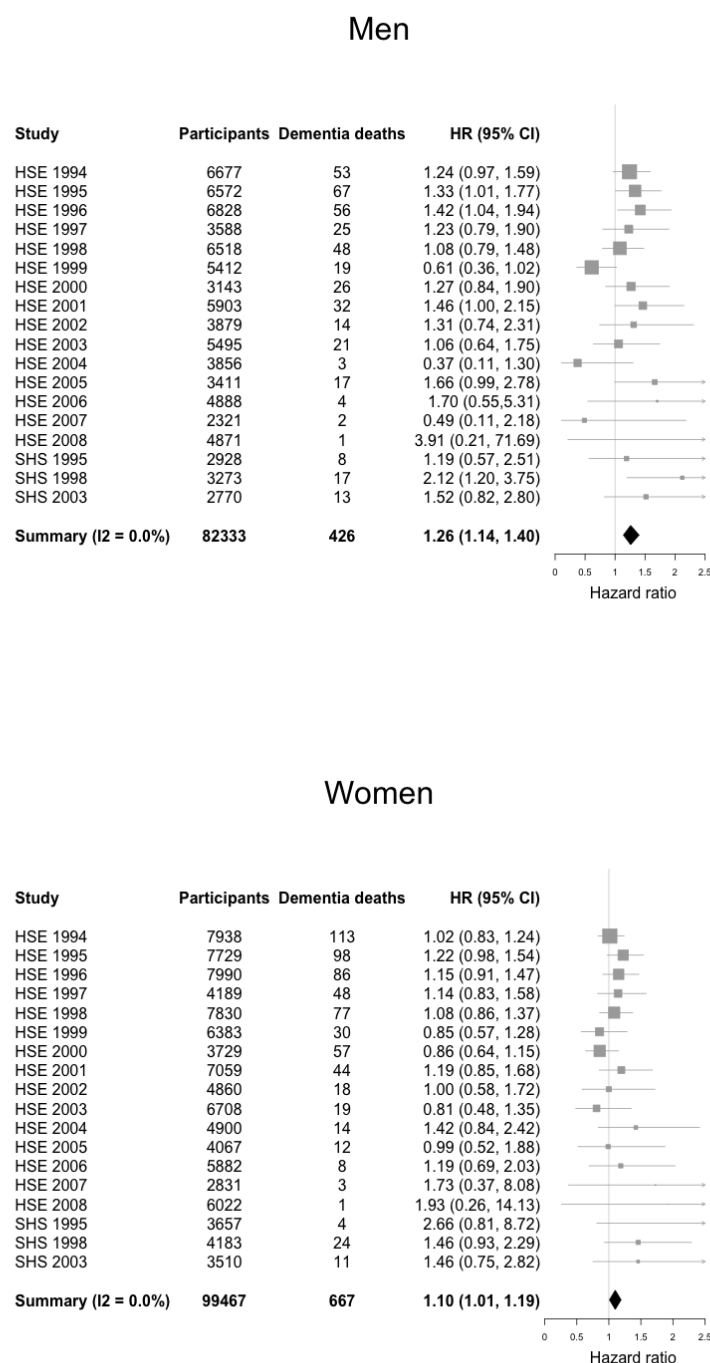


FIGURE 3. Scatterplot showing the secular trend (with 95% confidence interval) in height by birth year: individual participant meta-analysis of eighteen cohort studies from the Health Survey for England and the Scottish Health Survey (N = 181,800)

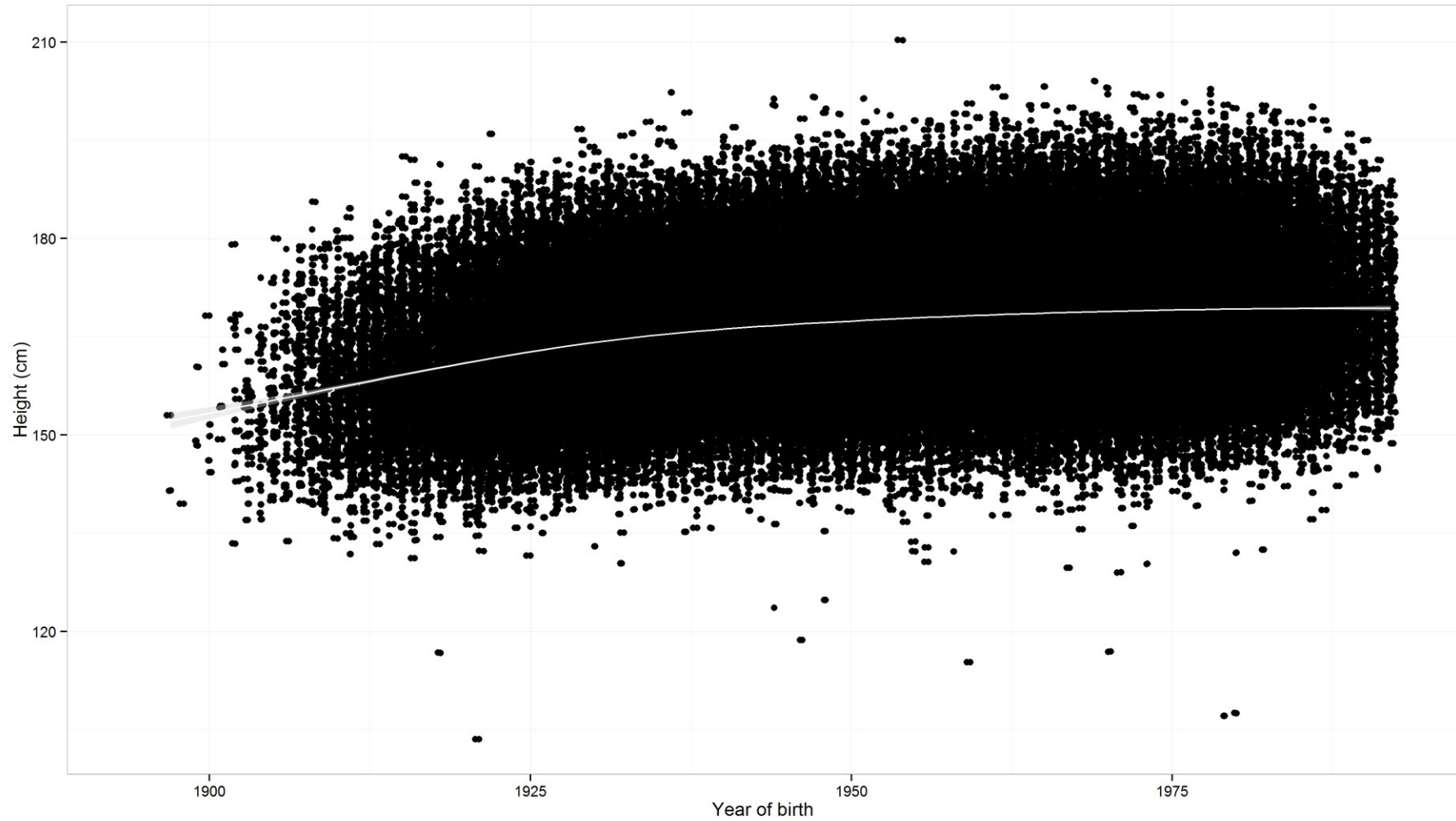


TABLE 1. Baseline characteristics of study members according to height quartile: individual participant meta-analysis of eighteen cohort studies from the Health Survey for England and the Scottish Health Survey (N = 181,800)

	Height ^{1,2}				
	Q ₁ (shortest)	Q ₂	Q ₃	Q ₄	Total N ³
MEN					
N	20398	20890	20667	20376	82333
Age [mean (SD)]	53.6 (18.8)	47.4 (17.6)	43.5 (16.7)	39.5 (15.0)	82333
Non-manual social class (%)	38.6	45.5	51.1	56.6	79251
Left school >16 years (%)	51.9	64.6	73.4	81.9	82290
White British (%)	85.3	90.4	92.8	94.7	82333
Body mass index [mean (SD)]	26.9 (4.4)	26.9 (4.2)	26.6 (4.2)	26.2 (4.0)	80281
Never smoker (%)	38.8	41.5	44.5	48.1	81972
Longstanding illness (%)	50.6	44.4	38.9	36.8	82314
Systolic blood pressure [mean (SD)]	137.9 (19.8)	135.1 (17.2)	133.6 (15.8)	132.4 (14.5)	53255
Serum cholesterol [mean (SD)]	5.7 (1.2)	5.7 (1.2)	5.5 (1.1)	5.4 (1.1)	27017
WOMEN					
N	24443	25266	24971	24787	99467
Age (mean [SD])	54.2 (19.6)	47.2 (17.6)	43.4 (16.6)	39.3 (14.8)	99467
Non-manual social class (%)	54.8	62.5	66.8	71.5	92695
Left school >16 years (%)	51.2	64.7	72.6	82.3	99410
White British (%)	85.8	90.9	93.0	94.5	99467
Body mass index [mean (SD)]	27.4 (5.6)	26.8 (5.3)	26.2 (5.2)	25.6 (4.9)	94147
Never smoker (%)	57.0	53.7	52.1	52.0	99130
Longstanding illness (%)	51.3	43.4	40.5	36.1	99450
Systolic blood pressure [mean (SD)]	135.4 (23.7)	130.4 (20.5)	127.1 (18.7)	124.7 (16.3)	63874
Serum cholesterol [mean (SD)]	5.9 (1.3)	5.8 (1.2)	5.6 (1.2)	5.4 (1.1)	31519

¹ Mean height and its SD across the studies were 174.4±7.3 cm in men and 161.0±6.8 cm in women

² Sex-specific height quartiles were calculated using the following cut-points: Men 179·3cm, 174·4cm, 169·6cm; Women 165·5cm, 161·1cm, 156·5cm

³ Total number of participants with complete data for each variable

TABLE 2. Hazard ratios (95% confidence intervals) for the association between height quartile and dementia-related death: individual participant meta-analysis of eighteen cohort studies from the Health Survey for England and the Scottish Health Survey (N = 181,800)

	Dementia deaths	N	Q ₄ ¹ (tallest)	Q ₃	Q ₂	Q ₁	Per SD disadvantage ²	P _{trend}
MEN								
Age-adjusted (basic model)	426	82333	1 (Ref.)	1.27 (0.75, 2.16)	1.32 (0.80, 2.17)	1.67 (1.05, 2.67)	1.26 (1.14, 1.40)	<0.001
+ Social class	425	79251	1	1.22 (0.72, 2.09)	1.23 (0.74, 2.03)	1.52 (0.95, 2.45)	1.21 (1.09, 1.34)	<0.001
+ Educational attainment	425	82290	1	1.20 (0.71, 2.05)	1.25 (0.76, 2.06)	1.56 (0.97, 2.50)	1.24 (1.11, 1.37)	<0.001
+ Ethnic group	426	82333	1	1.29 (0.76, 2.20)	1.34 (0.81, 2.22)	1.73 (1.08, 2.77)	1.27 (1.14, 1.41)	<0.001
+ Body mass index	413	80281	1	1.24 (0.73, 2.13)	1.30 (0.79, 2.16)	1.70 (1.06, 2.72)	1.29 (1.16, 1.44)	<0.001
+ Smoking status	426	81972	1	1.25 (0.71, 2.13)	1.28 (0.77, 2.11)	1.59 (0.99, 2.55)	1.25 (1.13, 1.39)	<0.001
+ Longstanding illness	426	82314	1	1.26 (0.74, 2.15)	1.30 (0.79, 2.15)	1.68 (1.05, 2.68)	1.26 (1.14, 1.40)	<0.001
+ Systolic blood pressure ³	275	49030	1	1.06 (0.51, 2.19)	1.22 (0.60, 2.49)	1.42 (0.76, 2.67)	1.30 (1.14, 1.49)	<0.001
+ Serum cholesterol ³	130	23911	1	0.59 (0.22, 1.59)	1.03 (0.26, 4.01)	1.11 (0.50, 2.46)	1.28 (1.03, 1.58)	0.025
Multivariable-adjusted ⁴	411	76927	1	1.15 (0.67, 1.98)	1.18 (0.71, 1.96)	1.50 (0.93, 2.43)	1.24 (1.11, 1.39)	<0.001
Early deaths excluded (multivariable adjusted) ^{4,5}	310	65455	1	1.15 (0.64, 2.07)	1.36 (0.77, 2.40)	1.44 (0.85, 2.45)	1.27 (1.12, 1.45)	<0.001
Non-missing sample (Age-adjusted)	411	76927	1	1.20 (0.70, 2.05)	1.26 (0.76, 2.08)	1.65 (1.03, 2.63)	1.27 (1.14, 1.41)	<0.001
WOMEN								
Age-adjusted (basic model)	667	99467	1 (Ref.)	1.40 (0.90, 2.19)	1.04 (0.66, 1.62)	1.22 (0.76, 1.97)	1.10 (1.01, 1.19)	0.031
+ Social class	617	86994	1	1.37 (0.87, 2.16)	0.96 (0.59, 1.57)	1.19 (0.73, 1.95)	1.11 (1.01, 1.19)	0.026
+ Educational attainment	667	99410	1	1.33 (0.85, 2.08)	0.96 (0.62, 1.50)	1.11 (0.70, 1.77)	1.07 (0.98, 1.16)	0.143
+ Ethnic group	667	99467	1	1.40 (0.90, 2.19)	1.04 (0.66, 1.64)	1.25 (0.78, 2.00)	1.11 (1.02, 1.20)	0.018
+ Body mass index	651	94147	1	1.56 (0.98, 2.48)	1.19 (0.75, 1.90)	1.49 (0.91, 2.44)	1.15 (1.05, 1.25)	0.002
+ Smoking status	666	99130	1	1.41 (0.90, 2.20)	1.04 (0.67, 1.62)	1.23 (0.78, 1.96)	1.10 (1.01, 1.19)	0.032
+ Longstanding illness	667	99450	1	1.43 (0.92, 2.24)	1.05 (0.68, 1.63)	1.25 (0.78, 2.00)	1.10 (1.01, 1.19)	0.033
+ Systolic blood pressure ³	431	62684	1	1.55 (0.87, 2.78)	1.10 (0.63, 1.90)	1.41 (0.85, 2.34)	1.09 (0.98, 1.21)	0.118
+ Serum cholesterol ³	195	27696	1	1.67 (0.75, 3.74)	1.44 (0.66, 3.16)	1.60 (0.75, 3.39)	1.05 (0.90, 1.22)	0.542
Multivariable-adjusted ⁴	601	82115 ⁶	1	1.48 (0.92, 2.39)	1.06 (0.64, 1.74)	1.35 (0.80, 2.28)	1.13 (1.03, 1.24)	0.011
Early deaths excluded (multivariable adjusted) ^{4,5}	495	74221	1	1.39 (0.81, 2.39)	0.95 (0.49, 1.85)	1.05 (0.45, 2.49)	1.10 (0.99, 1.22)	0.063
Non-missing sample (Age-adjusted)	601	82115 ⁶	1	1.50 (0.93, 2.42)	1.08 (0.63, 1.85)	1.38 (0.79, 2.39)	1.14 (1.05, 1.25)	0.003

¹ Sex-specific height quartiles were calculated using the following cut-points: Men 179.3cm, 174.4cm, 169.6cm; Women 165.5cm, 161.1cm, 156.5cm.

² Calculated using sex-specific standard deviations: Men 7.3cm; Women 6.8cm.

³ Data were only available for a subsample and therefore these covariates are not included in the multivariable model.

⁴ Model adjusted for age, occupational social class, educational attainment, self-reported ethnic group, body mass index, smoking status, self-reported longstanding illness, and year of birth.

⁵ Deaths occurring within the first five years of follow up dropped. No events occurred in HSE 2006-2008 so these surveys were excluded.

⁶ No events occurred in HSE 2008 so this survey was excluded from this model

TABLE 3. Articles examining the association between height (body height, knee height, or leg length) and dementia: individual participant meta-analysis of eighteen cohort studies from the Health Survey for England and the Scottish Health Survey (N = 181,800)

Article	Design	Population	Exposure	Outcome	Methods	Main results
Huang et al. (2008) ¹²	Prospective (average 5.4 years of follow-up)	2798 men and women in the USA aged ≥65 years	Knee height and arm span measured at baseline – continuous measures and quartiles	Two-stage screening culminating in clinical diagnosis of dementia (N=412)	Cox proportional hazards models	Age-, race-, and APOE status-adjusted HR per cm increase in knee height: Men 0.93 (95%CI 0.81, 1.07); Women 0.84 (0.74, 0.96) HR additionally adjusted for education, income and self-reported health: Men 0.95 (0.83, 1.10); Women 0.88 (0.77, 1.00) OR (95%CI) of dementia adjusted for age, socioeconomic status, and geographical area of birth in tallest vs shortest quartile: 0.51 (0.35, 0.74). Approximately similar results for AD and vascular dementia. Mean height (SD) in incident cases of probable AD 1.5m (0.1) vs other participants 1.6m (0.09), p=0.009. N.B. The main exposure examined in the paper was head circumference.
Beeri et al. (2005) ¹¹	Prospective (over three decades of follow up)	1892 men living in Israel aged 76-95 years	Height measured in 1963 as part of the Israeli Ischemic Heart Disease Project – quartiles	Two-phase screening culminating in clinical diagnosis of dementia (N=309)	Logistic regression	OR (95%CI) of dementia adjusted for age, socioeconomic status, and geographical area of birth in tallest vs shortest quartile: 0.51 (0.35, 0.74). Approximately similar results for AD and vascular dementia.
Borenstein Graves et al. (2001) ³⁰	Prospective (average 3.8 years of follow-up)	1869 Japanese American men and women aged ≥65 years	Height measured at baseline – continuous	Two-phase screening culminating in clinical diagnosis of AD (N=59)	t-test	Mean height (SD) in incident cases of probable AD 1.5m (0.1) vs other participants 1.6m (0.09), p=0.009. N.B. The main exposure examined in the paper was head circumference.
Kim et al. (2008) ³⁴	Cross-sectional	916 Korean men and women aged ≥65 years	Leg length measured at initial study visit – continuous measure	Clinical diagnosis of dementia (N=128)	Logistic regression	Age-adjusted OR per 7cm decrease in leg length, 95%CI: Men 1.17 (0.87, 1.56); Women 1.51 (1.19, 1.92). OR adjusted for age, heart disease, hypertension, and diabetes: Men 0.99 (0.82, 1.38); Women 1.34 (1.02, 1.75). OR (95%CI) shortest vs tallest quartile: Men 0.41 (0.2, 0.9); Women 0.38 (0.4, 1.5).
Petot et al. (2007) ³³	Cross-sectional	Men and women in the USA aged ≥60 years (341 controls, 239 cases)	Height measured at the time of the study – quartiles	Clinical diagnosis (both cases and controls were assessed)	Case-control	Age- and sex-adjusted OR (95%CI) for dementia in short height group (>1SD shorter than mean for their sex) vs others: 1.57 (1.11, 2.22). OR (95%CI) adjusted for age, sex, education, mentally stimulating activities, physical exercise, oral disease, and parents' social class: 1.49 (1.04, 2.12). Monozygotic co-twin control analyses using height as a dichotomous variable: OR for the short height group (95%CI): 1.75 (0.51, 5.98). Similar analyses treating height as an ordinal variable (comparing exposure status within twin pairs) OR for the short height group (95%CI): 1.31 (0.85, 2.04).
Gatz et al. (2006) ³²	Cross-sectional	Swedish twins aged ≥65 years and alive in 1998 (HARMONY study; 3053 controls, 310 cases)	Height reported on mailed questionnaire – dichotomous variable	Two-phase screening culminating in clinical diagnosis of dementia	Case-control	Arm span and height were associated with MMSE and IADL scores but not SDQ. Age- and sex- adjusted OR (95%CI) for dementia per cm decrease in height: 1.09 (1.05, 1.14). OR (95%CI) adjusted for age, sex, education, smoking, alcohol consumption, pulse pressure, hypertension, and type 2 diabetes mellitus: 1.03 (0.97, 1.11). OR (95%CI) for dementia adjusted for age and education per 5cm decrease in leg length: Men 1.03 (0.64, 1.65); Women 1.80 (1.29, 2.51).
Jeong et al. (2005) ²⁶	Cross-sectional	235 Korean men and women aged ≥65 years	Arm span and height measured at the time of the study – continuous measure	Clinical diagnosis of dementia (N=46; stated as 19.6%) and assessment scales (MMSE, IADL, and SDQ)	Linear and logistic regression	Arm span and height were associated with MMSE and IADL scores but not SDQ. Age- and sex- adjusted OR (95%CI) for dementia per cm decrease in height: 1.09 (1.05, 1.14). OR (95%CI) adjusted for age, sex, education, smoking, alcohol consumption, pulse pressure, hypertension, and type 2 diabetes mellitus: 1.03 (0.97, 1.11). OR (95%CI) for dementia adjusted for age and education per 5cm decrease in leg length: Men 1.03 (0.64, 1.65); Women 1.80 (1.29, 2.51).
Kim et al. (2003) ³¹	Cross-sectional	746 Korean men and women aged ≥65 years	Arm span, leg length, and sitting height measured at the time of the study – continuous measure	Two-phase screening culminating in clinical diagnosis of dementia (N=110)	Logistic regression	OR (95%CI) for dementia adjusted for age and education per 5cm decrease in leg length: Men 1.03 (0.64, 1.65); Women 1.80 (1.29, 2.51).

AD = Alzheimer's disease; CI = confidence interval; HR = hazard ratio; IADL = instrumental activities of daily living scale; MMSE = Mini mental state examination; OR = odds ratio; SDQ = Samsung dementia questionnaire